**Practitioner's Docket No. U 014673-3** *PATENT*

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: MANNE SATYANARAYANA **REDDY**, et al
Serial No.: 10/608,781 Group No.: 1625
Filed: June 27, 2003 Examiner:
For: PROCESS FOR PREPARATION OF OPTICALLY PURE OR OPTICALLY ENRICHED SULFOXIDE COMPOUNDS, INCLUDING AMORPHOUS ESOMEPRAZOLE AND SALTS THEREOF

**Commissioner for Patents**
**P. O. Box 1450**
**Alexandria, VA 22313-1450**

## TRANSMITTAL OF CERTIFIED COPIES

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

| | |
|---|---|
| Country: | INDIA |
| Application Number: | 489/MAS/2002 |
| Filing Date: | JUNE 27, 2002 |
| Country: | INDIA |
| Application Number: | 493/MAS/2002 |
| Filing Date: | JUNE 27, 2002 |

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JANET K. CORD
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SIGNATURE OF PRACTITIONER

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*NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent, if the foreign application is referred to in the oath or declaration, as required by § 1.63."* 37 C.F.R. 1.55(a).

10/608,781
Group No.: 1625
U014673-3

**THE PATENTS ACT, 1970**

**It is hereby certified that annexed hereto is a true copy of Application, Complete Specification & Abstract of the extract of Patent Application No.489/MAS/2002, dated 27.06.2002 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.**

.....

.....**In witness thereof**

**I have hereunto set my hand**

**Dated this the 26th day of December 2003**
**5th day of Pausa, 1925(Saka)**

M. S. V

**(M.S. VENKATARAMAN)**
**ASSISTANT CONTROLLER OF PATENTS & DESIGNS**

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Cheque/~~D.D~~/P.O/~~D.D~~/on 27/6/02
Vide C.S.B. No. 4245

**FORM 1**

**THE PATENTS ACT, 1970**
**APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)**

We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

1. (a) that we are in possession of an invention titled "**Novel process for the preparation of enantiomers of Omeprazole, their salts and hydrates thereof**"
   (b) that the complete specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to us.
2. further declare that the inventors for the said invention are **Manne Satyanarayana Reddy, Muppa Kishore Kumar, Koilkonda Purandhar and Kikkuru Srirami Reddy.** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**
3. that we are the assignee of the true and first inventors
4. that our address for service in India is as follows;

   Dr. Manne Satyanarayana Reddy,
   Vice President-R&D
   Dr. Reddy's Laboratories Limited
   7-1-27, Ameerpet
   Hyderabad, A.P., 500 016
5. following declaration was given by the inventors.
   We, the true and first inventors for this invention declare that the applicant herein is our assignee

Signed)_____
Manne Satyanarayana Reddy,
H.No. 8-3-167/D/16,
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Near AG Colony,
Erragadda, Hyderabad-500 038.

Signed)_____
Muppa KishoreKumar,
LIG-34, Dharma Reddy Colony,
Phase-I,
KPHB,
Hyderabad-500 072.

Signed) K. Purandhar

Koilkonda Purandhar.
MIG – 129,
Balaji Nagar,
Kukatpally,
Hyderabad – 500 072.

Signed) K. Srirami reddy

Kikkuru Srirami Reddy.
Pedamakkena,
Sattenapalli.
Guntur Dt.
PIN: 500 402.

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application
   (a) complete specification (---17--- pages, in triplicate)
   (b) abstract of the invention (------01------ page, in triplicate)
   (c) drawings (------- pages, in triplicate)
   (d) fee Rs. 5000.00 (five thousand rupees only) in cheque bearing No.336086 dated June 13th 2002 drawn on HDFC Bank Limited, Lakdikapul, Hyderabad

We request that a patent may be granted to us for the said invention

Dated this 26th day of June 2002.

Signed) M. Sumy

Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr. Reddy's Laboratories Limited.

**FORM 2**

**THE PATENTS ACT, 1970**

# COMPLETE SPECIFICATION

**(SECTION 10)**

## Novel process for the preparation of enantiomers of Omeprazole, their salts and hydrates thereof

**Dr. Reddy's Laboratories Limited**

**an Indian Company having its registered office at**

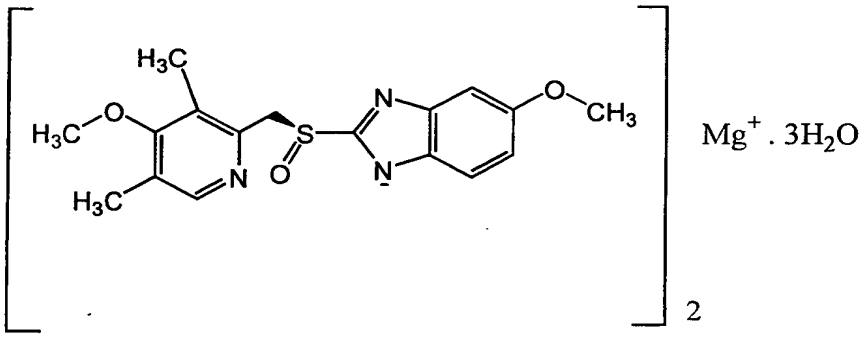
**7-1-27, Ameerpet**

**Hyderabad - 500 016, A.P., India**



The following specification particularly describes the nature of this invention and the manner in which it is to be performed:

The present invention relates to the novel process for the preparation of enantiomers of Omeprazole, their salts and hydrates thereof. The present invention is more specifically relates to (-) enantiomer of Omeprazole magnesium trihydrate salt i.e., Esomeprazole magnesium trihydrate salt, chemically known as (-) 5-methoxy-2- [[(4-methoxy-3, 5-dimethyl-2-pyridinyl)-methyl] sulphinyl]-1H-benzimidazole magnesium trihydrate salt. It is represented by the following formula (I).




Formula (I)

Omeprazole, and its therapeutically acceptable alkaline salts are described in EP 5129 and EP 124,495 respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as anitulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom i.e., can exist as an optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties, which will give an improved therapeutic profile.

The separation of the enantiomers of Omeprazole in analytical scale is described in J.Chromatography, 532 (1990), 305-19 and in preparative scale in DE 4035455.

**DE 4035455** discloses the process for the preparation of enantiomers of Omeprazole, Esomeprazole and its therapeutically active salts are claimed specifically. The process for

the preparation of enantiomers has been done by using diastereomeric ether, which is separated and thereafter hydrolyzed in an acidic solution.

**US 5,693,818** discloses the novel method to produce the single enantiomers of Omeprazole in neutral form, any isolated or characterized salt form and its analogues. The said patent particularly relates to sodium, calcium or magnesium salts of optically pure enantiomers of Omeprazole in 99.8% enantiomeric excess.

The process for the preparation of Esomeprazole comprises the reaction of 6-methoxy analog of Omeprazole with (R)-(-)-mandelic acid in chloroform to result the diastereomeric mixture, thus obtained mixture was subjected to reversed phase chromatography to get the more hydrophilic diastereomer. This was further reacted with aqueous sodium hydroxide solution in methanol using methyl formate to get the Esomeprazole with a purity of 94% enantiomeric excess and which was converted to sodium, magnesium or calcium salts in different solvents.

**US 5,948,789** discloses the process for the preparation of single enantiomers or an enantiomerically enriched form of Omeprazole by an asymmetric oxidation of pro-chiral sulphide with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base. The process for the preparation of sodium salt of Esomeprazole was disclosed in the said patent, which comprises reacting sulphide intermediate of Omeprazole with (+)-diethyl L-tartrate, titanium (IV) isopropoxide and di isopropyl ethylamine using cumene hydroperoxide as an oxidizing agent in ethyl acetate. Then after to the resulting sulphoxide was added sodium hydroxide and upon crystallization yielded the Esomeprazole sodium salt with a purity of 99.8% enantiomeric excess.

Several other references were also disclosed the process for the preparation of single enantiomers of Omeprazole with a considerable purity of enantiomeric excess.

The prior art references have some disadvantages for example the single enantiomers of Omeprazole obtained as per the process mentioned in USP 5,693,818 resulting in a syrup but not as crystalline products. The process mentioned in some other patents involves more number of reagents and processes are not recommendable for large-scale production.

The present invention provides a novel process for the preparation of single enantiomers of Omeprazole, their pharmaceutically acceptable salts and hydrates their of.

The present invention is simple, eco-friendly and cost effective process with a purity of high enantiomeric excess.

The present invention is more specifically relates to the preparation of Esomeprazole magnesium trihydrate salt, which comprises the novel resolution method using cheaper and commercially available Mandelic acid. Esomeprazole magnesium trihydrate salt produced in the present invention is having an optical purity of 99.8% enantiomeric excess.

The present invention also provides the process for the preparation of pharmaceutically acceptable salts of enantiomers of Omeprazole, particularly sodium and potassium salts and their hydrates.

**SUMMARY OF THE INVENTION:**

The present invention is relates to novel process for the preparation of enantiomers of Omeprazole, pharmaceutically acceptable salts and hydrates their of. The present invention more specifically relates to a process for the preparation of Esomeprazole magnesium trihydrate salt. The process for the preparation comprises, resolution of Omeprazole sodium using Mandelic acid and a chiral titanium complex in a suitable solvent to result the

titanium complex of mandelic acid salt of Esomeprazole. The said complex salt is reacted with sodium bicarbonate and subjected to racemisation in acetone to afford Esomeprazole in solid form , which is optionally converted to pharmaceutically acceptable salts in a solvent with high optical purity having a moisture content equivalent to trihydrate.

The process of the present invention is simple, eco-friendly and cost effective, hence can be well suited for large-scale production.

**DETAILED DESCRIPTION OF THE INVENTION:**

Accordingly, the novel process for the preparation of enantiomers of Omeprazole, pharmaceutically acceptable salts and hydrates, which comprises:

i) suspending Omeprazole sodium of formula (II) in ketone solvents such as acetone, ethyl methyl ketone, methyl isobutyl ketone or diethyl ketone, preferably acetone;

ii) adding diethyl tartrate, titanium (IV) isopropoxide and an organic base to the reaction mixture of step (i);

iii) adding mandelic acid to the reaction solution of step (ii) accompanied by stirring the mass for 15 minutes to 5 hours at an ambient temperature;

iv) filtering the separated solid of step (iii) to get the titanium complex of mandelic acid salt of formula (III);

v) suspending the titanium complex of mandelic acid salt obtained in step (iv) in a mixture of 5 % sodium bicarbonate solution and a chlorinated solvent such as chloroform, dichloromethane, dichloroethane or carbon tetrachloride, preferably dichloromethane;

vi) distilling the solvent from the reaction solution of step (v) under nitrogen atmosphere and accompanied by optional racemisation in a solvent such as acetone , ethylacetate or acetonitrile to get the compound of formula (IV);

vii) optionally isolating the formula (IV) in solid form by known methods;

viii) optionally converting formula (IV) into pharmaceutically acceptable salts such as magnesium , sodium or potassium and their hydrates of formula (V).

The organic base mentioned in the step (ii) of the above process is selected from triethyl amine, di isobutyl amine, di tertiary butyl amine or tri isobutyl amine, di isopropyl ethylamine, di isobutyl ethyl amine, preferably tri ethyl amine.

The (-) enantiomer of Omeprazole i.e., Esomeprazole is prepared as per the process mentioned above by using diethyl D-tartrate in step (ii) and the L (+) Mandelic acid in step (iii). Esomeprazole obtained in the present process is having a purity of >99.8% enantiomeric excess.

The (+) enantiomer of Omeprazole is prepared as per the process mentioned above by using diethyl L-tartrate in step (ii) and the D (-) Mandelic acid in step (iii) with a purity of >99.8% enantiomeric excess.

The racemisation in acetone mentioned in step (vi) is partial crystallization to separate the required single enantiomer in high purity. The solvent acetone is more suitable for separating the (+) and (-) enantiomers of Omeprazole because of the difference in their solubility levels.

The (-) enantiomer of Omeprazole can be isolate in a solid form with high optical purity by recrystallizing the crude compound in mixture of water and acetone. The detailed experimentation is described in experimental section.

The (-) and (+) enantiomers of Omeprazole are converted into their pharmaceutical acceptable salts by known methods in the art. The detailed experimentation is described in experimental section.

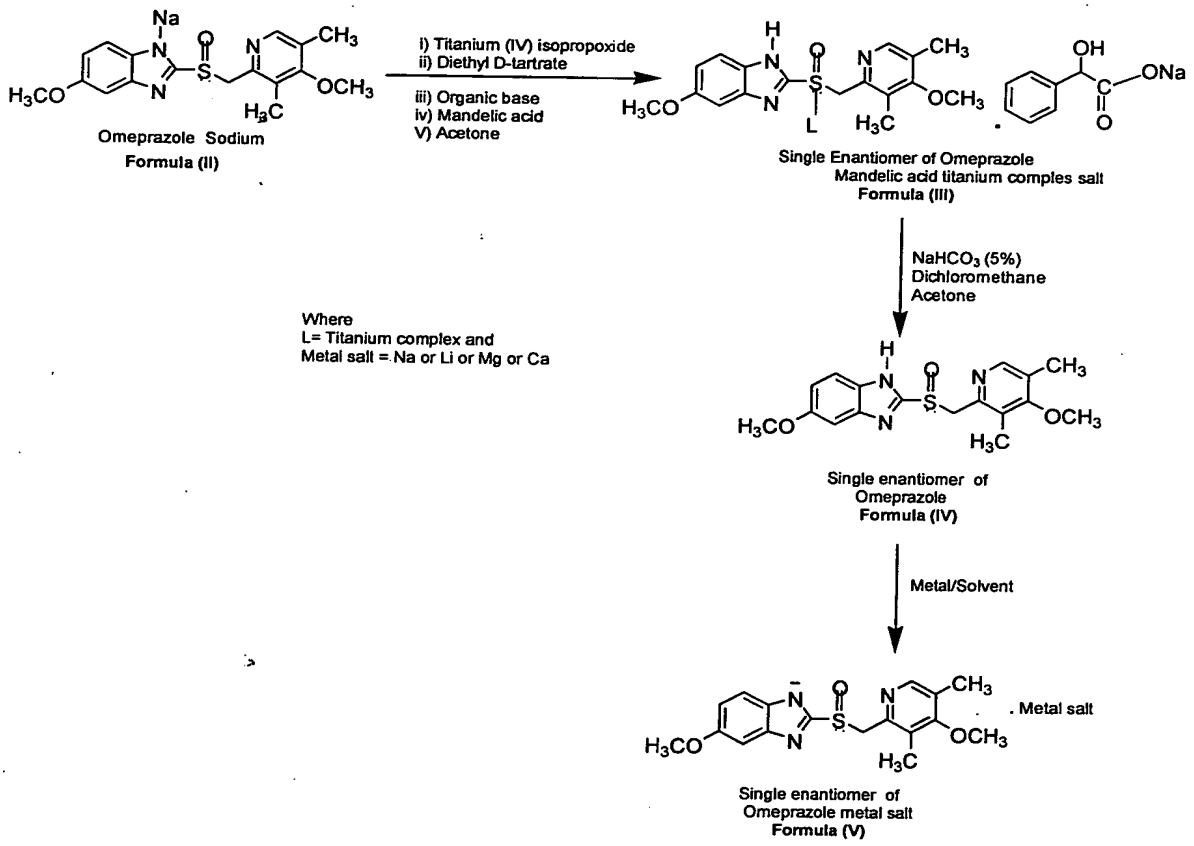
The Esomeprazole magnesium salt obtained in the present invention is having moisture content of 7.50% by KF method, which is equivalent trihydrate.

The other related analogs of Omeprazole being sulfoxides, have an asymmetric center in the sulfur atom exists the optical isomerism. The single enantiomers of well known sulfoxides moiety drugs, which includes Lansaprazole, Pantaprazole and Rabeprazole, belongs to similar therapeutically active group are prepared in above described process. All the compounds are obtained in high optical purity having >99.0% enantiomeric excess. Hence, the present novel process provides the process for the preparation of single enantiomers of Omeprazole and their analogs in high optical purity.

The present invention involves cheaper and commercially available mandelic acid for resoluting the racemic mixture of Omeprazole and their analogs to afford the single enantiomer with a purity of >99.0% enantiomeric excess.

The (-) enantiomer of Omeprazole is having an enhanced therapeutical activity over Omeprazole in the treatment of ulcerative diseases.

The process of the present invention can be schematically depicted as follows.




Omeprazole sodium of Formula (II) is reacted with Titanium (IV) isopropoxide, Diethyl tartrate, Mandelic acid in presence of a suitable organic base to afford the single enantiomer of titanium complex of mandelic acid salt of Formula (III). Thus, obtained salt is reacted with sodium bicarbonate and further racemisation in acetone gives single enantiomer of Omeprazole of formula (IV). The obtained optically pure enantiomer is further converted in to pharmaceutically acceptable salt of formula (V).

It is noteworthy to mention that Omeprazole sodium is prepared as per the process disclosed in the art. Omeprazole sodium is also outsourced in commercial quantities.

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

**Reference Example:**

**Preparation of Omeprazole sodium (Formula-II):**

Dissolved sodium hydroxide flakes (12.8 grams) in methanol (100 ml) and stirred for complete dissolution. Isopropyl alcohol (900 ml) was added and cooled the reaction mixture to 25-30$^{O}$C. Filter the solution through hi-flow bedded funnel and wash with isopropyl alcohol (100 ml). Charge Omeprazole (100 grams) to the clear filtered solution at an ambient temperature and stirred for 1-2 hours. The isolated product was filtered and washed with isopropyl alcohol (200 ml) followed by petroleum ether (200 ml), dried at atmospheric temperature to afford the sodium salt of Omeprazole (Weight: 100 grams).

**Example-1:**

**Preparation of Mandelic acid titanium complex salt of Esomeprazole (Formula III):**

Omeprazole sodium (100 grams) was suspended in Acetone (1.2 liter) and Diethyl D-tartrate (56.0 grams), Titanium (IV) isopropoxide (40.0 grams) and Triethylamine (82.0 grams) were added sequentially at a temperature of 35-40$^{O}$C. L(+) Mandelic acid (41.5 grams) was then added and further stirred for 15-30 minutes. The separated solid was filtered, washed with acetone (500ml) to afford the title compound.

[Weight: 80.0 grams, Chiral Purity: 99.78% (S-Isomer)]

**Example-2:**

**Preparation of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole (Esomeprazole-Formula IV):**

Mandelic acid titanium complex salt of Esomeprazole (75.0 grams, obtained in Example-1) was suspended in a mixture of dichloromethane (375 ml), 5% sodium bicarbonate solution (375 ml), further stirred for 15-30 minutes. The dichloromethane layer was separated from the resulting solution and the solvent was distilled off completely to get the title compound in residual mass.

[Weight: 37.0 grams, Chiral Purity: 99.85% (S-Isomer)]

**Example-3:**

**Preparation of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole magnesium trihydrate salt (Esomeprazole magnesium trihydrate salt-Formula -V):**

Magnesium metal (1.33 grams) and Dichloromethane (3.7 ml) was added to methanol (111 ml) and stirred for 1-2 hours. Cooled the mass to a temperature of 5-10$^{O}$C, added Esomeprazole (37.0 grams, obtained in example-2) and methanol (111.0 ml) accompanied by stirring for 15-30 minutes. The reaction mass was decomposed into water (666 ml) at a temperature of 5-10$^{O}$C in over a period of 45-60 minutes. The reaction mass was further stirred for 30-45 minutes to separate the solid mass. The solid mass was filtered, washed with water (222 ml). Thus, obtained compound was dissolved in methanol (222 ml) and filtered off the solution to separate the excess magnesium. The solvent was expelled from the filtrate to get the residual mass.

The residual mass was crystallized in Acetone (278 ml) at a temperature of 0-5$^{O}$C to afford optically pure Esomeprazole magnesium trihydrate salt.

[Weight: 11.5 grams, Chiral Purity: 100%, Optical rotation: -125$^{O}$ (c=0.5% methanol)]

The (-) enantiomer of Omeprazole magnesium dihydrate salt was similarly prepared as above by controlled drying process.

**Example-4:**

**Preparation of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2- pyridinyl) methyl]sulphinyl]-1H-benzimidazole Sodium trihydrate salt**

Sodium hydroxide flakes (4.5 grams) was added to methanol (50 ml) and stirred for 15-30 minutes. Cooled the mass to a temperature of 5-10$^{O}$C, Esomeprazole (25.0 grams, obtained as per example-2) and methanol (100.0 ml) were added and accompanied by stirring for 30-60 minutes. The solvent was expelled off completely from the reaction solution. Di isopropyl ether (150 ml) was added to the residual mass and further stirred for 30-60 minutes. Cooled the mass to a temperature of 0-5$^{O}$C and stirred for 30-60 minutes to separate the solid mass. The solid mass was filtered and dried at a temperature of 60-70$^{O}$C under vacuum to afford optically pure Esomeprazole Sodium trihydrate salt.

[Weight: 14.5 grams, Chiral Purity: 99.53 %, Optical rotation: + 42$^{O}$ (c=0.5% water)]

The (-) enantiomer of Omeprazole sodium dihydrate salt was similarly prepared as above by controlled drying process.

**Example-5:**

**Preparation of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole potassium salt**

Potassium hydroxide flakes (6.3 grams) was added to methanol (50 ml) and stirred for 15-30 minutes. Cooled the mass to a temperature of 5-10$^{O}$C, Esomeprazole (25.0 grams, obtained as per example-2) and methanol (100.0 ml) were added and accompanied by stirring for 30-60 minutes. The solvent was expelled off completely from the reaction solution. Di isopropyl ether (150 ml) was added to the residual mass and further stirred for 30-60 minutes. Cooled the mass to a temperature of 0-5$^{O}$C and stirred for 30-60 minutes to separate the solid mass. The solid mass was filtered and dried at a temperature of 60-70$^{O}$C under vacuum to afford optically pure Esomeprazole Sodium trihydrate salt.

[Weight: 12.0 grams, Chiral Purity: 100 %, Optical rotation: + 28.0$^{O}$ (c=1% water)]

The (-) enantiomer of Omeprazole sodium dihydrate salt was similarly prepared as above by controlled drying process.

**Example-6:**

**Preparation of (-)-5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole (in solid form):**

Esomeprazole (20.0 grams, obtained as per Example-2) was dissolved in a mixture of acetone (100 ml) , water (200 ml) and further stirred for 15-30 minutes. The pH of the mass was adjusted with caustic lye to 12 to13 accompanied by stirring for 30- 60 minutes. The reaction solution was subjected to carbon treatment at atmospheric temperature. Then, the pH was further adjusted to 7 to 8 with acetic acid. The reaction mass was cooled to a temperature of 5-10$^{O}$C and stirred for 1-2 hours to crystallize the solid mass. The solid

mass was filtered, washed with water (100 ml) and dried under vacuum at a temperature of 25-30$^{O}$C to a constant weight.

(Weight: 7.0 grams, Chiral Purity: 99.94%)

**Example-7:**

**Preparation of Mandelic acid titanium complex salt of (+) enantiomer of Omeprazole:**

Omeprazole sodium (10 grams) was suspended in Acetone (120 ml) and Diethyl L-tartrate (5.6 grams), Titanium (IV) isopropoxide (4.0 grams) and Triethyl amine (8.2 grams) were added sequentially at a temperature of 35-40$^{O}$C. D(-) Mandelic acid (4.2 grams) was then added and further stirred for 15-30 minutes. The separated solid was filtered, washed with acetone (50 ml) to afford the title compound.

[Weight: 7.50 grams, Chiral Purity: 98.01% (R-Isomer)]

The (+) enatiomer of Omeprazole and its salts such as magnesium, sodium or potassium were prepared in a similar method as mentioned in above examples.

**We Claim:**

1. A novel process for the preparation of enantiomers of Omeprazole, pharmaceutically acceptable salts and hydrates, which comprises:

   i) suspending Omeprazole sodium of formula (II) in ketone solvents such as acetone, ethyl methyl ketone, methyl isobutyl ketone or diethyl ketone, preferably acetone;

   ii) adding diethyl tartrate, titanium (IV) isopropoxide and an organic base to the reaction mixture of step (i);

   iii) adding mandelic acid to the reaction solution of step (ii) accompanied by stirring the mass for 15 minutes to 5 hours at an ambient temperature;

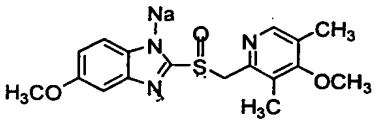
   iv) filtering the separated solid of step (iii) to get the titanium complex of mandelic acid salt of formula (III);

   v) suspending the titanium complex of mandelic acid salt obtained in step (iv) in a mixture of 5 % sodium bicarbonate solution and a chlorinated solvent such as chloroform, dichloromethane, dichloroethane or carbon tetrachloride, preferably dichloromethane;

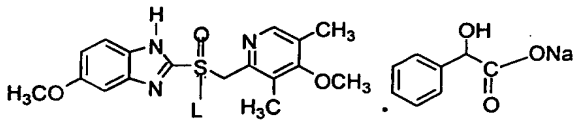
   vi) distilling the solvent from the reaction solution of step (v) under nitrogen atmosphere and accompanied by optional racemisation in a solvent such as acetone , ethylacetate or acetonitrile to get the compound of formula (IV);

   vii) optionally isolating the formula (IV) in solid form by known methods;

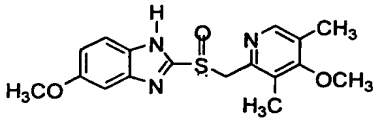
   viii) optionally converting formula (IV) into pharmaceutically acceptable salts such as magnesium , sodium or potassium and their hydrates of formula (V).



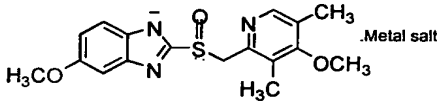
Formula (II)



Formula (III)



Formula (IV)



Formula (V)

Wherein metal = Mg, Na or K

2. The process according to claim 1, wherein the end product is (-) enatiomer of Omeprazole and its pharmaceutically acceptable salts.
3. The process according to claim 1, wherein the end product is (+) enatiomer of Omeprazole and its salts.
4. The process according to claim 1 & 2, wherein the end product is (-) enantiomer of Omeprazole magnesium salt.
5. The process according to claim 1 & 2, wherein the end product is (-) enantiomer of Omeprazole sodium salt.
6. The process according to claim 1 & 2, wherein the end product is (-) enantiomer of Omeprazole potassium salt.
7. The process according to claim 1 & 3, wherein the end product is (+) enantiomer of Omeprazole magnesium salt.
8. The process according to claims 1 & 4, wherein the end product is (-) enantiomer of Omeprazole magnesium trihydrate salt.

9. The process according to claims 1 & 8, wherein the optical purity of (-) enantiomer of Omeprazole magnesium trihydrate salt is >99.7% enantiomeric excess.

10. The process according to claim 1 of step (i), wherein the said ketone solvent is acetone.

11. The process according to claim 1 of step (ii), wherein the chiral ester is (-)-diethyl-D-tartrate in case of (-) enatiomer of Omeprazole .

12. The process according to claim 1 of step (ii), wherein the chiral ester is (+)-diethyl-L-tartrate in case of (+) enatiomer of Omeprazole.

13. The process according to claim 1 of step (ii), wherein the titanium complex is prepared from a titanium (IV) compound.

14. The process according to claims 1 & 13, wherein the titanium (IV) compound is a titanium (IV) alkoxide.

15. The process according to claims 1 & 14, wherein the titanium (IV) alkoxide is titanium (IV) isopropoxide.

16. The process according to claim 1 of step (ii), wherein the chiral resolution takes place in the presence of base.

17. The process according to claims 1 & 16, wherein the base is an organic base.

18. The process according to claims 1 & 17, wherein the base is an amine selected from di isopropyl ethyl amine or tri ethyl amine.

19. The process according to claim 1 of step (iii), wherein the chiral resoluting agent is mandelic acid.

20. The process according to claims 1 and 19, wherein the chiral resoluting agent is L(+) mandelic acid in case of (-) enantiomer of Omeprazole.

21. The process according to claims 1 and 19, wherein the chiral resoluting agent is D(-) mandelic acid in case of (+) enantiomer of Omeprazole.

22. The process according to claim 1 of step (v), wherein the said chlorinated solvent is dichloromethane.

23. The process according to claim 1 of step (vi), wherein the said solvent for racemisation is acetone.

24. A novel process for the preparation of enantiomers of Omeprazole, pharmaceutically acceptable salts and hydrates is substantially as herein described and exemplified.

Dated: 26th the day of June 2002

Signed)_____
Dr. Manne Satyanarayana Reddy,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.

## ABSTRACT

The present invention is relates to novel process for the preparation of enantiomers of Omeprazole, pharmaceutically acceptable salts and hydrates their of. The present invention more specifically relates to a process for the preparation of Esomeprazole magnesium trihydrate salt. The process for the preparation comprises, resolution of Omeprazole sodium using Mandelic acid and a chiral titanium complex in a suitable solvent to result the titanium complex of mandelic acid salt of Esomeprazole. The said complex salt is reacted with sodium bicarbonate and subjected to racemisation in acetone to afford Esomeprazole in solid form , which is optionally converted to pharmaceutically acceptable salts in a solvent with high optical purity having a moisture content equivalent to trihydrate.

The process of the present invention is simple, eco-friendly and cost effective, hence can be well suited for large-scale production.